ORGANIC LETTERS

2010
Vol. 12, No. 8
1716−1719

Regioselective and Stereoselective Cyclizations of Chloropolyols in Water: Rapid Synthesis of Hydroxytetrahydrofurans

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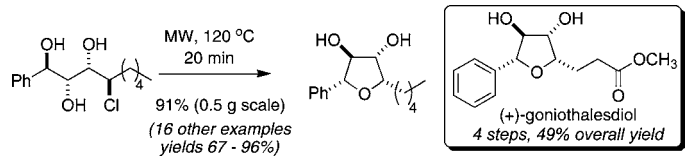
Received February 2, 2010

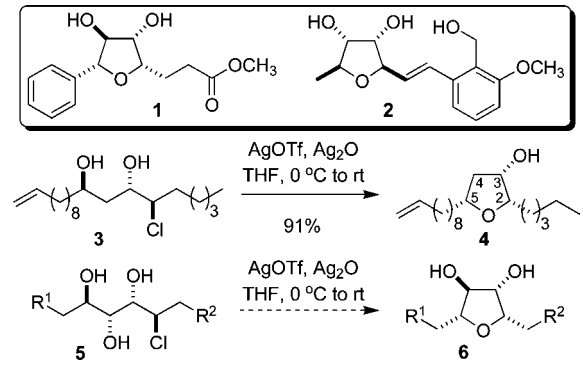
ABSTRACT



A concise, stereoselective synthesis of functionalized tetrahydrofuranols has been developed that involves heating readily available chloropolyols in water. These reactions are operationally straightforward and chemoselective for the formation of tetrahydrofurans, obviating the need for complicated protecting group strategies. The efficiency of this process is demonstrated in a short asymmetric synthesis of the natural product (+)-goniothalesdiol.

The prevalence of tetrahydrofuranols in biologically active natural products[1] continues to motivate the development of new synthetic methods to access these substances.[2,3] For example, a number of syntheses of the cytotoxic *Goniothalamus* styryllactones and their naturally occurring derivatives (e.g., goniothalesdiol (**1**), Scheme 1) have been reported,[4] and owing to a 100-fold increased potency over mean toxicity toward a variety of cancer cell lines,[5] varitriol (**2**) has attracted the attention of several synthetic chemistry groups.[6] Recently, we reported a rapid and stereochemically

Scheme 1. Naturally Occurring Tetrahydrofuranols and the Silver-Promoted Cyclization of Unprotected Chlorodiols



(1) (a) Bermejo, A.; Figadere, B.; Zafra-Polo, M.-C.; Barrachina, I.; Estornell, E.; Cortes, D. *Nat. Prod. Rep.* **2005**, 269. (b) Dutton, C. J.; Banks, B. J.; Cooper, C. B. *Nat. Prod. Rep.* **1995**, 165.

(2) For a recent review, see: Wolfe, J. P.; Hay, M. B. *Tetrahedron* **2007**, *63*, 261.

(3) For recent examples of tetrahydrofuran syntheses, see: (a) Friestad, G. K.; Lee, H. J. *Org. Lett.* **2009**, *11*, 3958. (b) Mitchell, T. A.; Zhao, C.; Romo, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5026. (c) Parsons, A. T.; Campbell, M. J.; Johnson, J. S. *Org. Lett.* **2008**, *10*, 2541. (d) Donohoe, T. J.; Williams, O.; Churchill, G. H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2869. (e) Wang, J.; Pagenkopf, B. *Org. Lett.* **2007**, *9*, 3703.

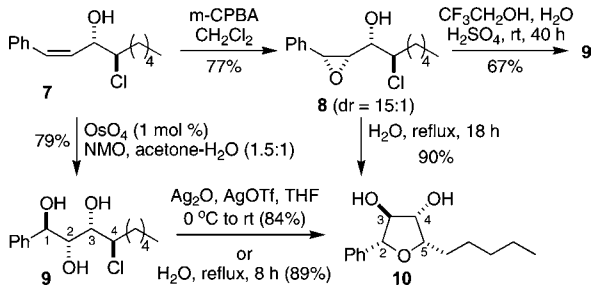
(4) For example, see: (a) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron* **2005**, *61*, 2471. (b) Carreño, M. C.; Hernández-Torres, G.; Urbano, A.; Colobert, F. *Org. Lett.* **2005**, *7*, 5517. (c) Prasad, K. R.; Gholap, S. L. *J. Org. Chem.* **2006**, *71*, 3643. (d) Ghosh, S.; Rao, C. N.; Dutta, S. K. *Synlett* **2007**, *9*, 1464. (e) Yoda, H.; Nakaseko, Y.; Takabe, K. *Synlett* **2002**, *9*, 1532. (f) Yadav, J. S.; Raju, A. R.; Rao, P. P.; Rajaiah, G. *Tetrahedron: Asymm.* **2005**, *16*, 3283. (g) Babjak, M.; Kapitán, P.; Gracza, T. *Tetrahedron Lett.* **2002**, *43*, 6983. (h) Murga, J.; Ruiz, P.; Falomir, E.; Carda, M.; Peris, G.; Marco, J.-A. *J. Org. Chem.* **2004**, *69*, 1987.

10.1021/ol100260z
Published on Web 03/18/2010

flexible synthesis of 2,5-disubstituted 3-hydroxytetrahydrofurans that involves a silver-promoted cyclization of unprotected chlorodiols (e.g., **3**).[7] While this process affords the corresponding tetrahydrofurans (e.g., **4**) in excellent yield, a notable drawback is the requirement for stoichiometric quantities of both AgOTf and Ag_2O. During our efforts to expand the scope of this reaction and investigate the cyclizations of unprotected chlorotriols (e.g., **5** → **6**), we found that a variety of chloropolyols undergo direct cyclization to the corresponding tetrahydrofuranol by simply heating them in water. Herein we describe the discovery, optimization, and scope of this environmentally friendly and economic process as well as its application in the concise asymmetric synthesis of goniothalesdiol (**1**).

The chlorotriols required for this work were readily available from alkenyl chlorohydrins,[8] prepared through the addition of vinyllithium reagents to α-chloro aldehydes.[9] For example, hydroxyl-directed epoxidation[10] of chlorohydrin **7** afforded epoxide **8** (Scheme 2), the treatment of which

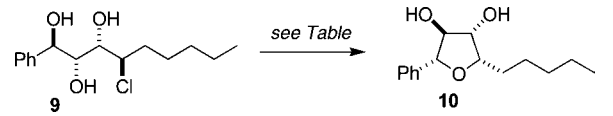
Scheme 2. Synthesis of the Dihydroxytetrahydrofuran **10**



with dilute acid provided chlorotriol **9** as the major diastereomer (dr = 8:1).[11] Alternatively, triol **9** could be accessed directly from the alkenylchlorohydrin **7** via hydroxyl-directed dihydroxylation (dr = 20:1). While it was gratifying to find that our optimized conditions (AgOTf, Ag_2O)[7] effected the desired cyclization (i.e., **9** → **10**), surprisingly, the spectral data derived from the resultant tetrahydrofuranol **10** were identical to those of a minor byproduct observed during optimization of the epoxide opening (i.e., **8** → **9**). For example, when the epoxychlorohydrin **8** was treated with aqueous H_2SO_4 (0.5 M) for 18 h, a mixture of the triol **9** and its C1 epimer (dr = 3:1, 40% combined yield) were produced along with the tetrahydrofuran **10** and its C2 epimer (dr = 3:1, <5% combined yield). This observation prompted us to re-examine the epoxide opening, whereupon it was eventually discovered that heating the epoxychlorohydrin **8** in aqueous H_2SO_4 (0.5 M) afforded the 3:1 mixture of tetrahydrofurans in 67% yield (not shown). Moreover, repetition of this reaction *without added acid* (i.e., simply heating **8** in water) provided the tetrahydrofuranol **10** in 90% yield. As tetrahydrofuran formation presumably proceeds via the triol **9**, this later material was also heated in water (8 h), which resulted in clean formation of the expected tetrahydrofuran **10** as a single stereoisomer (89% yield).

In an effort to reduce the reaction time required for tetrahydrofuran formation and assess the importance of water to this process, cyclization of the chlorotriol **9** was repeated in a variety of solvents using microwave heating. As indicated in Table 1, tetrahydrofuran **10** was produced in

Table 1. Microwave-Assisted Cyclization of the Chlorotriol **9**[a]



entry	solvent	time (min)	temp[b] (°C)	yield[c] (%)
1	H_2O	10	120	91
2	H_2O	5	180	90
3	DMSO	15	120	82
4	$PhCH_3$	30	120	0
5	DMF	10	120	25[d]
6	CH_3CN	25	120	55[d]
7	CH_3OH	10	120	90
8	pH 7 buffer	20	120	86

[a] A 0.1 M solution of **9** was heated as indicated in a sealed vial in a Biotage Initiator 2.5 (400 W magnetron) microwave reactor. [b] Internal temperature measured with a vertically focused IR temperature sensor. [c] Isolated yield of **10**. [d] Product formation accompanied by decomposition of **9** and/or **10**.

moderate to excellent yield in all solvents except toluene, although no significant quantities of product were observed within 1 h at temperatures below 100 °C. Notably, the cyclization can also be carried out in aqueous pH 7 buffer in nearly identical yield (86% yield) to that obtained in pure water, conditions that may be beneficial for acid-sensitive substrates. To demonstrate the practical utility of this process, 0.5 g of the chlorotriol **9** was heated for 20 min at 120 °C in 3 mL of water to provide, after simple decantation, 0.39 g (91%) of the tetrahydrofuranol **10**.

In order to explore the scope of this reaction, a number chlorodiols, triols, and tetrols[12] were subjected to brief microwave heating in water (Table 2). In general, these microwave-assisted cyclizations proceeded in excellent yield regardless of the configuration or functionalization of the starting material. As indicated in entries 1 and 2, cyclization of the silyl-protected chlorotetrols **12** and **14** led to the

(5) (a) Malmstrøm, J.; Christophersen, C.; Barrero, A. F.; Oltra, J. E.; Justica, J.; Rosales, A. *J. Nat. Prod.* **2002**, *65*, 364. (b) Mayer, A. M. S.; Gustafson, K. R. *Eur. J. Cancer* **2004**, *40*, 2676.

(6) (a) McAllister, G. D.; Robinson, J. E.; Taylor, R. J. K. *Tetrahedron* **2007**, *63*, 12123. (b) Clemens, R. T.; Jennings, M. P. *Chem. Commun.* **2006**, 2720. (c) Kumar, V.; Shaw, A. K. *J. Org. Chem.* **2008**, *73*, 7526. (d) Palík, M.; Karlubíková, O.; Lasiková, A.; Kozízek, J.; Gracza, T. *Eur. J. Org. Chem.* **2009**, 709.

(7) Kang, B.; Mowat, J.; Pinter, T.; Britton, R. *Org. Lett.* **2009**, *11*, 1717.

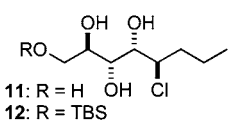
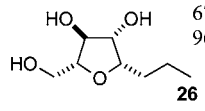
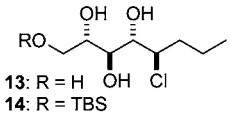
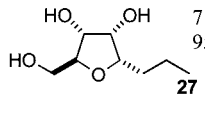
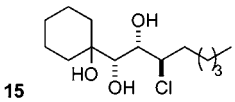
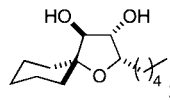
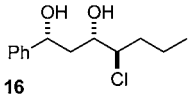
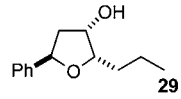
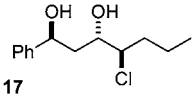
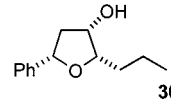
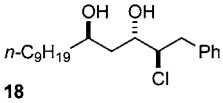
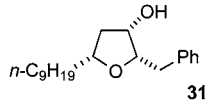
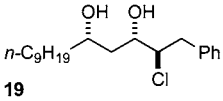
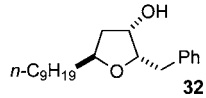
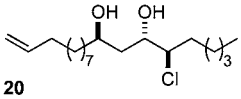
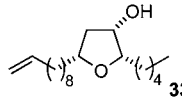
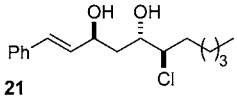
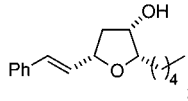
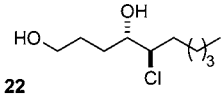
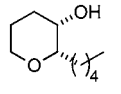
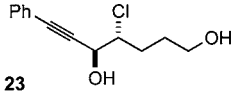
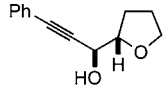
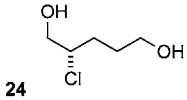
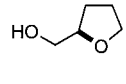
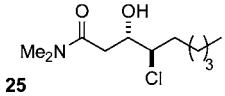
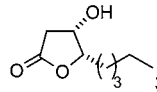
(8) Kang, B.; Britton, R. *Org. Lett.* **2007**, *9*, 5083.

(9) (a) Brochu, M. P.; Brown, S. P.; Macmillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108. (b) Halland, N.; Braunton, A.; Bachmann, S.; Marigo, M.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2004**, *126*, 4790. (c) Amatore, M.; Beeson, T. D.; Brown, S. P.; MacMillan, D. W. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5121.

(10) Adam, W.; Wirth, T. *Acc. Chem. Res.* **1999**, *32*, 703.

(11) That this process involves double inversion at C1 suggests the intermediacy of a tetramethylenechloronium ion. See: Olah, G. A.; Peterson, P. E. *J. Am. Chem. Soc.* **1968**, *90*, 4675.

Table 2. Microwave-Assisted Cyclization of Chloropolyols[a]

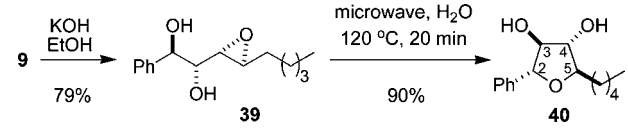
entry	chlorohydrin	product	yield[b]
1	 **11**: R = H **12**: R = TBS	 **26**	67% from **11** 96% from **12**
2	 **13**: R = H **14**: R = TBS	 **27**	71% from **13** 95% from **14**
3	 **15**	 **28**	94%
4	 **16**	 **29**	93%
5	 **17**	 **30**	82%
6	 **18**	 **31**	81%
7	 **19**	 **32**	80%
8	 **20**	 **33**	87%
9	 **21**	 **34**	88%
10	 **22**	 **35**	<10%
11	 **23**	 **36**	85%
12	 **24**	 **37**	86%
13	 **25**	 **38**	89%[c]

[a] A solution/suspension of chlorohydrin in H_2O (0.1 M) was heated in a sealed vial at 120 °C in a CEM Discover LabMate microwave reactor for 20 min. [b] Isolated yield. [c] Reaction carried out at 80 °C in CH_3OH-H_2O.

C-linked pentoses **26** and **27**, respectively, whereby concomitant removal of the silyl protecting group occurs under the reaction conditions (i.e., generation of HCl). Remarkably, simply heating the chlorotetrols **11** or **13** (entries 1 and 2) in water, which could lead to formation of epoxides,[8] oxetanes,[13] tetrahydrofurans,[14] and/or tetrahydropyrans, resulted in selective formation of the corresponding *C*-linked pentoses **26** and **27**, respectively. This result is consistent with the fact that the structurally simplified chlorodiol **22** (entry 10) failed to produce appreciable amounts of tetrahydropyran or epoxide. Thus, this experimentally straightforward process obviates the need for protecting groups on ancillary alcohol functions.[15] Tertiary alcohols were also readily converted to tetrahydrofurans (entry 3), as were a variety of configurationally and structurally unique chlorodiols (entries 4−9). Notably, both allylic and propargylic alcohols (entries 9 and 11) were compatible with the reaction conditions, and all cyclizations proceeded in yields better than those obtained employing our $AgOTf/Ag_2O$ protocol and in much less time (20 min vs 12 h). As indicated in entries 11 and 12, the hydroxymethyltetrahydrofuran subunit **37**, common to many of the potently cytotoxic annonaceous acetogenins,[1a] is accessible through this cyclization strategy. It was also found that the 3-hydroxy-γ-lactone **38** (entry 13) could be prepared as a single configurational isomer through briefly heating the readily available aldol adduct **25**.

While we were pleased with the generality and efficiency of the cyclization reactions summarized in Table 2, access to the chlorohydrin starting materials **11**−**25** via the addition of lithium enolates or vinyl lithium reagents to α-chloroaldehydes invariably leads to 1,2-*anti*-chlorohydrins.[7,8] Consequently, the cyclizations of chloropolyols derived from these substances are limited to the production of 2,3-*syn*-tetrahydrofuranols (e.g., **29**−**34**). Due to this limitation, we were inspired by Jamison's work on 6-*endo*-selective epoxide opening reactions in aqueous media[16] to explore the 5-*endo*-epoxide opening of epoxydiols, readily available from chloropolyols through treatment with base. For example, reaction of the chlorotriol **9** with KOH in EtOH afforded the epoxydiol **39**. We were delighted to find that brief heating (120 °C) of this material in water effected smooth conversion to the corresponding tetrahydrofuranol **40**, which was produced as a single diastereomer (Scheme 3). Overall, this

Scheme 3. Microwave-Assisted Cyclization of Epoxydiol **39**



epoxide formation/5-*endo*-epoxide opening sequence results in net retention of configuration at C5 and is thus a stereochemically complementary process to the direct cy-

(12) See the Supporting Information for the preparation of chloropolyols depicted in Table 1 and the stereochemical assignment of all compounds.

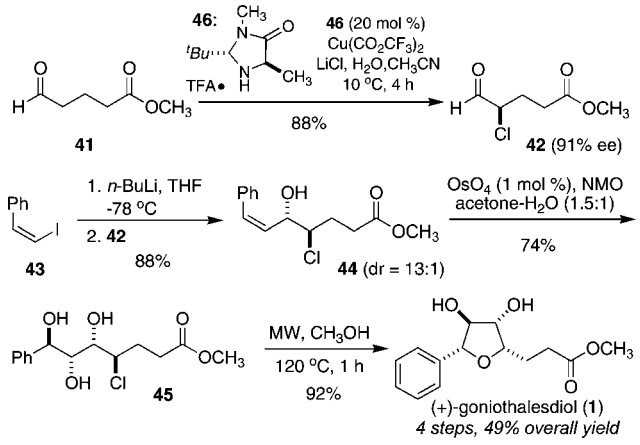
(13) For selected examples, see: (a) Morihira, K.; Hara, R.; Kawahara, S.; Nishimori, T.; Nakamura, N.; Kusama, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1998**, *120*, 12980. (b) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. *J. Am. Chem. Soc.* **2007**, *129*, 2269.

(14) For selected examples of tetrahydrofuran formation via displacement of secondary alkyl chlorides see refs 7, 13b, and: (a) Cekovic, Z.; Cvetkovic, M. *Tetrahedron Lett.* **1982**, *23*, 3791. (b) Sato, M.; Uchimaru, F. *Chem. Pharm. Bull.* **1981**, *29*, 3134.

clizations highlighted in Table 2. Further investigations that address the scope and utility of this microwave-assisted 5-*endo*-epoxide opening reaction are currently ongoing in our laboratory.

Finally, the efficiency of this chloropolyol cyclization strategy was demonstrated in a short synthesis of goniothalesdiol (**1**)[17] that initiated with the asymmetric α-chlorination of commercially available methyl 5-oxopentanoate (**41**) (Scheme 4). Unfortunately, the prolinamide-catalyzed organocatalytic α-chlorination method developed by Jørgensen[9b] and effectively employed by us in previous natural product syntheses[7,8,18] proved sluggish on the oxoester **41** and provided the desired α-chloro aldehyde **42** in modest yield and enantioselectivity (40% ee). Presumably, epimerization of the α-chloro product **42** occurs during the extended (20 h) reaction times required for full conversion of **41**. We were delighted to find, however, that MacMillan's *SOMO-activated aldehyde α-chlorination reaction*,[9c] that employs the imidazolidinone catalyst **46**, chosen in part for its lack of reactivity with the α-chloro products,[9c] provided the desired α-chloro aldehyde **42** in good yield and enantiomeric excess (91% ee). Treatment of the resultant chloroaldehyde **42** with the lithium anion derived from (*Z*)-2-phenyl-1-iodoethene (**43**) and subsequent dihydroxylation (dr = 8:1) afforded the chlorotriol **45** as the major diastereomer in 74% isolated yield. Microwave heating of this material in methanol gave (+)-goniothalesdiol (**1**) as a single configurational isomer. The spectral data (^{1}H NMR, ^{13}C NMR, HRMS, $[\alpha]_D$, IR)[19] derived from (+)-**1** were in complete agreement with those reported for the natural product.[4,17] It is noteworthy that this four-step synthesis of (+)-**1** compares well with those reported in the literature that range in length from 10 to 16 linear steps.[4]

Scheme 4. Total Synthesis of (+)-Goniothalesdiol (**1**)



In summary, we have developed a concise and stereochemically flexible approach to functionalized tetrahydrofuranols that involves simply heating readily available chloropolyols in water. Notably, this operationally straightforward reaction is both high yielding and regioselective for the formation of tetrahydrofurans. Thus, complicated protecting group strategies can be avoided, as displacement of the chloride by ancillary alcohol functions does not occur at any appreciable rate under these reaction conditions. The efficiency of this approach to functionalized tetrahydrofuranols was also demonstrated in a short (four-step) synthesis of the natural product goniothalesdiol (**1**). The application of this methodology to the synthesis of more structurally complex tetrahydrofuran-containing natural products is currently underway in our laboratory, and the results of these efforts will be reported in due course.

Acknowledgment. Research supported by NSERC-Canada and Merck Frosst Canada Ltd., Michael Smith Foundation for Health Research (B.K.), and NSERC CGS (B.K.). We thank Prof. Glenn Sammis (UBC) for generously allowing us use of his microwave reactor.

Supporting Information Available: Characterization data and detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The formation of oxepane was also inefficient following this protocol. For example, microwave heating of 6-chloro-1-hexanol in H_2O provided oxepane (10%), 1,6-hexanediol (20%), and 7-oxa-1,13-tridecanediol (30%).

(16) See, for example: (a) Simpson, G. L.; Heffron, T. P.; Merino, E.; Jamison, T. F. *J. Am. Chem. Soc.* **2006**, *128*, 1056. (b) Heffron, T. P.; Jamison, T. F. *Synlett* **2006**, *14*, 2329. (c) Morten, C. J.; Jamison, T. F. *J. Am. Chem. Soc.* **2009**, *131*, 6678. (d) Morten, C. J.; Byers, J. A.; Van Dyke, A. R.; Vilotijevic, I.; Jamison, T. F. *Chem. Soc. Rev.* **2009**, 3175.

(17) Isolation of goniothalesdiol: Cao, S.-G.; Wu, X.-H.; Sim, K.-Y.; Tan, B. K. H.; Pereira, J. T.; Goh, S.-H. *Tetrahedron* **1998**, *10*, 2143.

(18) Mowat, J.; Gries, R.; Gries, G.; Khaskin, G.; Britton, R. *J. Nat. Prod.* **2009**, *72*, 772.

(19) Certain resonances in the ^{13}C NMR spectrum of (+)-**1** recorded in $CDCl_3$ were found to shift slightly depending on concentration. The ^{13}C NMR spectrum of a 0.04 M solution of (+)-**1** was identical to that reported for both natural[17] and synthetic[4] goniothalesdiol. The specific rotation for synthetic (+)-**1** ($[\alpha]^{25}_D$ +7.2 (*c* 0.2, EtOH)) was consistent with the value reported in ref 17 for natural goniothalesdiol ($[\alpha]^{25}_D$ +7.5 (*c* 0.23, EtOH)).